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REVIEW

First episode schizophrenia

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Schizophrenia is a chronic psychiatric condition. Patients with schizophrenia present clinically with psychotic, negative and cognitive symptoms, which can become evident late in adolescence or in early adulthood. The peak age for presentation is 20 years in males and 25 years in females. This chronic condition follows a relapsing remitting course, and eventually results in a chronic state of residual symptoms and functional impairment.

Keywords: hallucinations, psychiatric condition, psychotic, schizophrenia, social withdrawal

Introduction

Schizophrenia is a chronic psychiatric condition. Patients with schizophrenia present clinically with psychotic, negative and cognitive symptoms, which can become evident late in adolescence or in early adulthood. The peak age for presentation is 20 years in males and 25 years in females. This chronic condition follows a relapsing remitting course, and eventually results in a chronic state of residual symptoms and functional impairment.

As the name indicates, first-episode schizophrenia refers to individuals who have formally presented with symptoms, have been evaluated and have received a diagnosis of probable or definitive schizophrenia. "First episode schizophrenia" is a clinical and research term often used to identify and emphasise special issues which arise when working with this specific population. Despite pessimism about the prognosis, it has been suggested in recent studies that early intervention can improve the long-term outcome of the disorder. Thus, the idea is that intervention at, or prior to, the onset of the first episode might improve the response to antipsychotic treatment, and thus the long-term course of the disorder.

Stages of schizophrenia

Four stages of schizophrenia are described by Insel.

Stage 1: Risk stage

Identifiable risk factors, for example, genetic vulnerability, a family history of schizophrenia and environmental exposure, are considered with respect to vulnerable individuals.

Stage 2: Prodrome of schizophrenia

The prodrome indicates a period before the full manifestation of a psychotic illness, during which patients first experience changes in their emotions, cognition or behaviour which may indicate a deviation from the normal level of functioning. Prodromal symptoms include decreased concentration and attention, a depressed mood, sleep disturbances, anxiety, social withdrawal, suspiciousness and irritability. Changes in thought include bizarre ideas which are not necessarily delusional in nature. The behavioural changes may include social isolation and impairment in functioning.

Stage 3: Onset of psychosis

The development of frank psychotic symptoms marks the formal onset of first episode schizophrenia. This stage could be present for some time, but is only formally addressed when medical attention is sought. This phase is characterised by frank psychotic symptoms, and can include hallucinations, delusions and disorganised thinking and behaviour, as well as psychomotor abnormalities. Negative symptoms and cognitive symptoms can also be present in this stage.

Stage 4: Chronic disability stage

Stage 4 is characterised by chronic social, occupational and functional disability. The life expectancy of patients living with schizophrenia is reduced by approximately 25 years.

There is a prevalence of 1% of schizophrenia in the general population, and both genetic and environmental factors have been implicated in the aetiology of the disease. Genetic factors contribute 80% to the risk of schizophrenia developing.

A number of chromosomal regions have been linked to the risk of developing the disease. Schizophrenia aggregates in families, and having an affected family member increases the risk of the disease developing substantially.

Numerous types of environmental exposure have also been implicated as risk factors in the development of schizophrenia. Environmental risk factors linked to a higher likelihood of developing schizophrenia include:

- A history of obstetric and perinatal complications, a history of winter births, as well as older paternal age at conception.
- Childhood trauma and abuse, and parental separation or death during childhood or adolescence, have also been linked to an increased risk of developing the disease.

Table 1: The clinical symptom domains of schizophrenia

Positive symptoms	Negative symptoms	Cognitive symptoms	Mood symptoms	Neuromotor symptoms
• Delusions • Hallucinations • Disorganised speech • Disorganised behaviour	• Affective blunting • Alogia • Avolition • Anhedonia • Social withdrawal	• Attention deficit • Memory deficit • Executive functioning deficit	• Depression • Irritability • Hopelessness • Suicidality • Anxiety • Agitation • Hostility	• Catatonia • Stereotypic movements • Dystonia • Hypokinaesia • Dyskinaesia

Other important risk factors which may increase the risk of schizophrenia developing in adolescents and young adults are:

- *Living in a densely populated urban environment:* Estimates of the increased risk of the urban environment as a causal risk factor for the development of schizophrenia are as high as 30%.
- *Social adversity:* Social adversity relating to discrimination or cultural isolation can predispose young adults to developing the disorder. It was demonstrated in an ecological study conducted in England that adolescents from a minority group who grew up in a neighbourhood less populated by the same minority group had a higher risk of developing schizophrenia than minority adolescents living in neighbourhoods that were more greatly populated by the same minority group.
- *Cannabis use in early adolescence:* Individuals with a genetic predisposition to developing schizophrenia display an exaggerated psychotic response when exposed to cannabis. The early initiation of cannabis use correlates with an increased risk, as well as an earlier age of onset of psychosis. The use of cannabis by the age of 15 in a study conducted in New Zealand was associated with a more than fourfold increase in the risk of developing schizophrenia by the age of 26 years.

Clinical presentation of first episode schizophrenia

Social isolation, psychotic symptoms and impairment in functioning may be present for some time before the patient makes contact with mental health services. Patients may also present with aggressive, and violent or suicidal behaviour.

The first presentation of psychosis may be frightening and distressing, not only for the patient, but also for families. The patient may be perplexed. Family and carers typically suffer distress, fear and confusion in relation to the patient's erratic and aggressive behaviour. Patients and carers often have difficulty dealing with the stigma and guilt associated with mental illness.

Early intervention in first episode psychosis is important in alleviating the distress and anxiety associated with the psychotic symptoms, as well as reducing the risk of suicide.

The patient with first episode psychosis is often distressed, not only about changes to his or her social patterns, but also by his or her symptoms. Hallucinations and delusions can cause considerable distress and anxiety, mixed with feelings of hopelessness, shame, entrapment and a feeling of being out of control. Patients often suffer from depression, feel hopeless and have feelings of loss. First episode psychosis also places patients at risk, or is associated with, risk-taking behaviour. Psychosis is also linked to substance use disorders. Between 20% and 60% of patients have a substance use disorder at some stage during the course of the illness.

The clinical symptom domains of schizophrenia are grouped according to various clusters (Table 1).

Duration of untreated psychosis

The period between the onset of the psychotic symptoms and the initial intervention for treatment of the acute psychotic episode, also referred to as the duration of untreated psychosis (DUP),is an important aspect and an area of increased research in the literature on first episode schizophrenia. The term "first episode schizophrenia" is often misleading when considered from the perspective of disease onset as these patients usually only present in times of crisis. Thus, the disease process may have been present for some time. An accurate history may reveal that the patient has been symptomatic for quite some time.

It was found in a meta analysis of DUP that the average DUP was nine months, but may be as long as two years. The long DUP could represent the resistance and barriers to initial care for persons who become psychotic. Delays in accessing treatment could either be because individuals do not understand the nature of their psychotic symptoms, or as a result of psychological factors, such as denial, lack of support, motivation, or because of fear of stigmatisation.

DUP has been an area of increasing research, especially regarding its role as a modifiable prognostic indicator for future long-term outcomes beyond the initial treatment episode. A correlation between the length of DUP and treatment outcome has been shown in studies on DUP, as a longer DUP predicts a poorer outcome. According to the hypothesis on a longer DUP, the DUP may be neurotoxic and alters the central nervous system in a way that renders the patient less responsive to treatment. Thus, patients with psychosis which is untreated for a longer period may not achieve the same level of recovery as those who received treatment sooner. However, current data in support of this hypothesis are mixed.

DUP is one of the predictors of the initial response to antipsychotic medication, where a shorter DUP is predictive of a better likelihood of antipsychotic response.

Shortening DUP is a measurable outcome of efforts to shorten the time between the diagnosis of schizophrenia and treatment of the psychotic symptoms. The advantage of recognising the

Table 2: Diagnostic criteria for schizophrenia, according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

A. Two or more of the following, each present for a significant portion of time during a one-month period, or less if successfully treated. At least one of these must be 1, 2 or 3:

1. Delusions
2. Hallucinations
3. Disorganised speech, e.g. frequent derailment or incoherence
4. Grossly disorganised or catatonic behaviour
5. Negative symptoms, i.e. diminished emotional expression or avolition.

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas (such as work, interpersonal relations or self-care) is markedly below the level achieved prior to the onset (or when the onset occurs in childhood or adolescence, there is failure to achieve the expected level of interpersonal, academic or occupational functioning).

C. Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms, or less if successfully treated, which meet criterion A (i.e. active-phase symptoms), and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may manifest through only negative symptoms, or by two or more symptoms listed in Criterion A which are present in an attenuated form, e.g. odd beliefs and unusual perceptual experiences.

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either:

1. No major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or
2. If mood episodes have occurred during the active-phase symptoms, they have been present for the minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance, e.g. a drug of abuse or a medication, or another medical condition.

F. If there is a history of an autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least one month, or less if successfully treated.

The following course specifiers are only to be used after a one-year duration of the disorder, and if they are not in contradiction to the diagnostic course criteria. Specify if:

- *First episode, currently in an acute episode:* First manifestation of the disorder meeting the defining diagnostic symptoms and time criteria. An "acute episode" is a period in which the symptom criteria are fulfilled
- *First episode, currently in partial remission: "Partial remission"* is a period during which an improvement after a previous episode is maintained, and in which the defining criteria of the disorder are only partially fulfilled
- *First episode, currently in full remission:* "Full remission" is a period after a previous episode, during which no disorder-specific symptoms are present
- *Multiple episodes, currently in an acute episode:* "Multiple episodes" may be determined after a minimum of two episodes, i.e. after a first episode, a remission, and a minimum of one relapse
- *Multiple episodes, currently in partial remission*
- *Multiple episodes, currently in full remission*
- *Continuous:* Symptoms fulfilling the diagnostic symptom criteria of the disorder remain for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course
- *Unspecified*

Specify if with catatonia

Specify current severity: Severity is rated according to a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganised speech, abnormal psychomotor behaviour and negative symptoms. Each of these symptoms is rated for its current severity (most severe in the last seven days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe).
Note: A diagnosis of schizophrenia can be made without using this severity specifier

significance of DUP is that it could reveal potential interventional strategies which might improve the outcome.

Differential diagnosis

The first episode schizophrenia patient can present with a number of symptoms which may be consistent with a schizophrenia prodrome, including a longstanding history of attention difficulties, a recent history of cognitive decline, social withdrawal and psychotic symptoms. However, these symptoms could also be explained in terms of major depression with psychotic features, bipolar disorder, substance use disorder and post-traumatic stress disorder, as well as autistic spectrum disorders. A number of non-psychiatric conditions have also been associated with psychosis, for example, metabolic and endocrine disorders, infective disorders, nutritional deficiency states, poison, toxins, and trauma and neoplasms. Thus, it is important to exclude these conditions before making a diagnosis of schizophrenia.

Management and treatment

An increasing body of evidence suggests that early and effective management in the critical early years of the disorder can improve the long-term outcome for schizophrenia. The treatment of first episode schizophrenia is of critical importance in that it may establish the long-term course of the illness and the acceptability of ongoing treatment in the years ahead.

A comprehensive approach to obtaining collateral information from all sources is required when assessing first episode psychosis (Table 2). Complete physical and special investigations are also

necessary. It is well-known that people with schizophrenia have a reduced life span. Therefore, attending to the physical needs of the individual with first episode psychosis through early assessment and ongoing monitoring during treatment should be routine (Table 3).

Table 3: The assessment of schizophrenia

Evaluate the causes of the psychotic episode
Interview individuals close to the patient, if feasible
Verify the diagnosis
Complete the psychiatric and general medical history and status
Identify co-morbid psychiatric and medical conditions, such as: • Substance use, e.g. marijuana • Infectious diseases, e.g. syphilis and HIV
Evaluate the patient's general medical health
Evaluate the suicide risk
Assess the likelihood of dangerous, impulsive or aggressive behaviour
Identify the patient's strengths and limitations
Assess the baseline values which may be affected by the antipsychotic treatment, such as: • Vital signs • Weight, height, body mass index and waist circumference • Cognition (MMSE) • Diabetes risk factors • Hyperprolactinaemia • The lipid profile • An electrocardiogram and determine serum potassium and magnesium levels • Pregnancy and sexually transmitted disease
Consider brain imaging for patients with a new onset of psychosis, or atypical clinical presentation
Engage in therapeutic alliance

MMSE: The Mini-Mental State Examination, HIV: human immunodeficiency virus

Treatment objectives are to reduce the morbidity and mortality of the disorder by decreasing the frequency and severity of the psychotic episodes, and also to improve the functional capacity and quality of life of individuals.

Pharmacological schizophrenia treatment reduces the symptoms and prevents relapse, whereas the psychosocial approach focuses on forging treatment engagement and compliance, as well as enhancing self-efficacy, and social and occupational functioning.

Pharmacotherapy with antipsychotic medication continues to be the cornerstone of treatment in first episode psychosis. The goals of pharmacotherapy include the reversal of positive symptoms, as well as relapse prevention. Secondary goals include a reduction in the negative symptoms, and in the depressive symptoms if they are present. It is also important to target cognitive symptoms and quality of life.

Antipsychotic medication is most effective in decreasing the positive symptoms, and is more effective in first episode psychosis than in multi-episode cases, with between 50–70% of patients achieving positive symptom remission. It has been revealed in studies that patients with first episode psychosis demonstrate a greater therapeutic response and require lower doses of medication than patients in the chronic stages of illness, indicating pharmacological sensitivity. However, this response to pharmacological treatment in patients with first episode illness has not led to a high rate of recovery.

The absence of a previous therapeutic response or side-effects to previous medication use is an important aspect in first episode patients. Acute and long-term treatment goals and side-effect profiles need to be balanced. It is important to remember that these patients are neuroleptically naïve, and thus are vulnerable to experiencing side-effects from the medication use. Therefore, the aim is start at the lowest possible therapeutic dose, and to gradually increase it, as appropriate (Table 4).

Table 4: Commonly prescribed antipsychotic medication

Antipsychotic medication	Equivalent doses mg/day
First generation	
Haloperidol	0.5–5
Trifluoperazine	5–30
Chlorpromazine	100–400
Second generation	
Risperidone	2–6
Olanzapine	5–20
Quetiapine	150–750
Aripiprazole	15–30
Ziprasidone	80–160

First-generation antipsychotic agents are fairly effective in reducing the positive symptoms of hallucinations and delusions. However, these medications are minimally effective in reducing negative and cognitive symptoms, and also cause side-effects, such as extrapyramidal symptoms and tardive dyskinesia, with long-term use.

Common side-effects of second-generation antipsychotic agents include weight gain, dyslipidaemia, hypertension, insulin resistance and metabolic syndrome. Cardiac rhythm disturbances can occur, especially prolongation of the QT interval. Important investigations which need to be conducted prior to commencement of the medication include measuring body mass index and blood pressure, as well as performing an electrocardiogram.

The results of large-scale studies, in which the effectiveness of first- and second-generation antipsychotic agents in schizophrenia were compared, appeared to indicate that the latter were no more effective than the former, and were not associated with a better cognitive or social outcome.

Many patients with first episode schizophrenia can achieve full remission after their first episode has been successfully treated. The degree of impairment does not change the need for ongoing antipsychotic medication. First episode schizophrenia patients are typically relieved after the acute psychotic episode resolves, and often attempt to place the experience behind them by discontinuing treatment and stopping medication. To prevent relapse, maintenance antipsychotic treatment is

as important for first episode schizophrenia patients as it is for patients with chronic schizophrenia. The use of a long-acting or depot antipsychotic medication to address poor compliance with treatment by these patients is a treatment option worthy of consideration. Promising results have been demonstrated in studies, though limited in number, in which the use of depot antipsychotic use in first-episode schizophrenia patients was investigated.

As far as psychosocial interventions are concerned, patients with first episode schizophrenia have been found to benefit from psychoeducation surrounding the illness, cognitive behavioural therapy, supportive therapy, social skills training, family support and supported employment. Educating the family on the illness is also very important.

However, it is concerning that despite responding well to treatment, most patients stop their medication within the first year. It was found in naturalistic follow-up studies that only 25% of first episode schizophrenia patients took their antipsychotic treatment consistently for the first year after starting treatment. Noncompliance with the medication is one of the greatest predictors of relapse.

First episode schizophrenia patients are especially reluctant to accept a formal diagnosis of schizophrenia, or any other similar disorder with the associated stigma of having an illness that requires ongoing treatment. Many factors contribute to this poor compliance, including efficacy problems, the side-effects of treatment, barriers to treatment access and illness-related factors.

Finally, more than a century after schizophrenia was defined as a progressive illness with a deteriorating course and negative prognosis, the focus has shifted to the early identification of, and intervention in, the disorder. It is postulated that early intervention and diagnosis in the disease process may limit the cognitive, social and functional impairments caused by the disorder.

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